

REMARKS

In connection with applicants' Request for Continued Examination (RCE), applicants respectfully request entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.114, and in light of the remarks which follow.

STATUS OF CLAIMS

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 remain in this application. Claims 3-7, 10, 15-19, 22, 29-31, 34, 58-62 and 65 have been cancelled by the foregoing amendment, without prejudice or disclaimer, which Claims 36-55 were previously cancelled. Claims 1, 8, 9, 11, 13, 20, 21, 23, 25, 32, 33, 56, 63, 64, 67 and 82 have been amended hereinabove. Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are under examination. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81 have been withdrawn from consideration as drawn to non-elected subject matter. However, the withdrawn claims have been amended to be commensurate in scope with the examined claims as amended so that they may ultimately be rejoined.

STATEMENT OF SUBSTANCE OF INTERVIEW

Applicants acknowledge and thank Examiners Lau and Jiang for the courtesy of the personal interview granted to the inventor, Nicholas S. Bodor, and to applicants' undersigned representative, on June 10, 2009.

At the interview, applicants' representative indicated that an RCE would be filed. The claim language was discussed and it was agreed that support for the word "free" would be investigated and the claim clarified in this respect, if necessary. It was also proposed that in order to expedite prosecution, the independent claims be amended to recite only a particular amorphous cyclodextrin, namely hydropropyl- β -cyclodextrin, for which data was discussed, as well as a weight ratio range of cladribine to the cyclodextrin of from about 1:10 to about 1:16 (as set forth in, for

example, Claim 6); these suggestions were looked upon favorably by the Examiners following a detailed discussion, first of the references relied upon by the Examiner and then of the Van Axel Castelli et al. , *J. Pharm.Sci.* 2008 submitted at the interview. The Van Axel Castelli et al. publication, a further copy of which is submitted herewith and listed on the accompanying Form PTO-1449, was shown to fully support the data in the specification for the claimed subject matter, to distinguish the instant complex from physical mixtures and to show the correctness of applicants' previous arguments with respect to the obviousness rejection based on Schultz et al. in view of Baert et al. Rather than repeating these discussions in detail, in this interview summary, applicants will repeat these discussions in detail in the remarks below. Finally, applicants provided several recent internet news reports concerning clinical trials of the product, further copies of which are appended.

DISCUSSION OF CLAIM AMENDMENTS

Claim 1 has been amended to specify "the amorphous cyclodextrin hydroxypropyl- β -cyclodextrin," rather than "an amorphous cyclodextrin"; this feature was previously recited, for example, in original Claim 4. Claim 1 has been further amended to specify that the weight ratio of cladribine to said amorphous cyclodextrin in said composition is from about 1:10 to about 1:16; this feature was previously recited, for example, in original Claim 6. As for the use of the word 'free' in association with "cladribine," the expression "free cladribine" simply means cladribine not in the inclusion complex; see page 7, lines 24-25, where "free cladribine" is clearly defined. Therefore, it is appropriate to retain this word in the claims; amorphous free cladribine is associated with the amorphous cyclodextrin as the non-inclusion complex (b) while there is no significant amount of free crystalline cladribine in the composition. As for the subject matter cancelled from Claim 1 or from any of the other claims, applicants of course reserve the right to file a continuing application thereon.

Claims 3-7 have been cancelled as either outside the scope of the claims or redundant in light of the amendment of Claim 1.

Claims 8 and 9 have been amended so that they depend from Claim 1, which contains the features of original Claim 7, and Claim 10 has been cancelled as outside the scope of amended Claim 1.

A minor linguistic amendment has been made to Claim 11 to make it more consistent with amended Claim 1.

Claim 13 has been amended to be commensurate in scope with Claim 1.

Claims 15-19 have been cancelled as either outside the scope of Claim 13 as amended or redundant in light of the amendment of Claim 13; Claims 20 and 21 have been amended so that they depend from Claim 13; and Claim 22 has been cancelled as outside the scope of amended Claim 13. All of these amendments are consistent with the amendment of Claim 1.

A minor linguistic amendment has been made to Claim 23 to make it more consistent with amended Claim 13.

Claim 25 has been amended to be commensurate in scope with Claim 1.

Claims 29-31 and 34 have been cancelled as either outside the scope of Claim 25 as amended or redundant in light of the amendment of Claim 25.

Claims 32-33 have been amended to depend from Claim 25, which contains the features of the claim upon which they previously depended.

Claim 56 has been amended to be consistent with Claim 1. Claims 58-62 and 65 have accordingly been cancelled as outside the scope of amended Claim 56 or redundant in light of the amendment of Claim 56. The dependencies of Claims 63 and 64 have been amended accordingly.

A minor linguistic amendment has been made to Claim 67 to make it more consistent with amended Claim 56.

Finally, Claim 82 has been amended so that it depends from Claim 1 and the language has been amended to specify the amorphous cyclodextrin hydroxypropyl- β -cyclodextrin consistent with Claim 1.

It is apparent from the foregoing that no new matter has been introduced by the amendments made.

FILING DATES ACCORDED TO CLAIMS

Applicants thank the Examiner for considering their remarks, particularly with respect to the international filing date. The PCT filing date of March 26, 2004 has been accorded to Claims 12, 66, 83, 85 and 89, while all other claims are deemed to be entitled to the February 4, 2004 filing date of U.S. Provisional Appln. No. 60/541,247.

ELECTIONS/RESTRICTIONS

As noted above, applicants have amended the withdrawn claims to be commensurate in scope with the product claims, so that the withdrawn claims can be ultimately rejoined.

OBJECTIONS WITHDRAWN

The Examiner's withdrawal of the previous objections to the specification is noted, with appreciation.

REJECTIONS WITHDRAWN

The withdrawal of the previous rejections under 35 U.S.C. §§ 112, second paragraph, and 102(b) are likewise noted, with appreciation.

CLAIM REJECTIONS - 35 U.S.C. § 103

Claims 1-12, 56-66 and 82-83 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. US Patent No. 6,194,395 in view of Baert et al. WO 97/18839, both previously made of record. It is submitted that this rejection cannot be maintained against any of the claims now in this application.

As explained at the interview, Schultz et al. describe two kinds of cyclodextrin formulations of cladribine, i.e., "soluble aqueous formulations of cladribine with

cyclodextrin solubilizers which are injectable in humans, as well as oral solid dosage forms containing a mixture of cladribine and cyclodextrins." (Emphasis added). See col., 1, lines 6-10, of the Schultz et al. patent. Applicants do not dispute the fact that Schultz et al. disclose hydroxypropyl- β -cyclodextrin (HP β CD), which is amorphous, but Schultz et al. disclose crystalline cyclodextrins as well. Indeed, Schultz et al. teach aqueous formulations containing a cladribine/HP β CD complex in solution for injectable use. On the other hand, Schultz et al. clearly teach that their solid oral dosage forms are mixtures of cladribine and cyclodextrin as set forth not only in col. 1, lines 8-10 ("oral solid dosage forms containing a mixture of cladribine and cyclodextrin") but also in col. 5, lines 50-64. There it is indicated that the solid oral dosage forms may be prepared as disclosed in Baert et al. WO 97/18837; this is in fact the only method disclosed by Schultz et al. for preparing the solid oral dosage forms. In col. 5, beginning at line 52, it is stated that "solid mixtures of the cyclodextrins with the active ingredient are prepared via melt-extrusion....the cladribine active ingredient and the cyclodextrins are mixed with other optional ingredients and then heated until melting occurs. The mixture is then extruded through an extruder having one or more nozzles." As set forth in col. 6 of the Schultz et al. patent, a typical oral dosage form has a formulation containing, as a milled extrudate, 1 mg to 15 mg of cladribine and 100 to 500 mg of cyclodextrin, and as excipients, 100 to 300 mg of microcrystalline cellulose, 10 to 200 mg of crospovidone, 1 to 5 mg of colloidal silicon dioxide and 2 to 10 mg of sterotex. Schultz et al. do not disclose or suggest to the ordinary skilled pharmaceutical scientist solid oral formulation of cladribine/cyclodextrin complexes as claimed herein. As noted at the interview, and as will be explained in detail below with reference to the Van Axel Castelli et al. article, the characteristics of a complex and a physical mixture are distinctly different; Schultz et al.'s solid mixtures of cladribine and cyclodextrin cannot be assumed to be the same as applicants' product, which is a complex cladribine-cyclodextrin complex. Even if the broad ratios of Schultz et al.'s mixtures encompass the ratios in applicants' complexes, having the same ratio does not give a physical mixture the same properties as a complex, a fact which is clearly shown by the Van Axel Castelli et al. document discussed in detail below.

As further noted at the interview, the Baert et al. WO document, incorporated by reference in Schultz et al., for its melt-extrusion method of making solid oral dosage forms, describes amorphous materials and solid solutions but does not teach or suggest that its solid dosage form products include amorphous cyclodextrin-drug complexes. On the contrary Baert et al. teach that:

(a) Prior art problems are solved by Baert et al. by the use of a melt-extrusion process to form solid mixtures comprising one or more cyclodextrins and insoluble active ingredients (Emphasis added; see page 3, lines 7-9).

(b) The compounds suitable for use in Baert et al.'s process "are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said one or more active ingredients with the cyclodextrin or cyclodextrins" (page 4, lines 5-7).

(c) Baert et al. teach that the characteristics of their products are different from those of a product obtained in water, since it is stated on page 6, lines 15-19:

It will be appreciated by a person skilled in the art that mixing two or more solids, i.e., one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together will give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

(d) Baert et al.'s process uses very high temperatures; note Table 1 on page 12, where several different drugs are mixed with HP β CD and melt-extruded, with temperatures of around 280°C being utilized and the products in every case as noted on page 13, lines 5-6, being solid solutions.

(e) Baert et al. do not mention cladribine; indeed, applicants have previously shown that cladribine is known to decompose at the high temperatures used by Baert et al. and thus cladribine falls in the group of compounds Baert et al. teaches are unsuitable for use in their process [point (b) above].

(f) Baert et al. in no way teach or suggest that their products contain complexes.

The unsuitability of Baert et al.'s temperatures and hence for the Baert et al. process as applied to cladribine with cyclodextrin, specifically with HP β CD, is furthermore proved by data in the Van Axel Castelli et al. article, as discussed in more detail below.

Also at the interview, to provide background with respect to drug/cyclodextrin complexation, applicants brought to the Examiners' attention, the Loftsson and Brewster cyclodextrin review article previously made of record in applicants' Third Information Disclosure Statement; see Loftsson et al., "Pharmaceutical Application of Cyclodextrins. 1. Drug Solubilization and Stabilization," *Journal of Pharmaceutical Sciences*, Vol. 85, No. 10, pp. 1017-1025, 1996, American Pharmaceutical Association and the American Chemical Society, US. The Loftsson and Brewster review article shows that it was known in the art that:

(a) Cyclodextrin/drug complexation typically is carried out in aqueous media, not by mixing in the absence of water (page 1020, left column, first full paragraph).

(b) This complexation involves many different forces (van der Waals, hydrogen bonding, etc.) and the use of water is essential to the formation of complexes (page 1018, right column, second full paragraph to page 1020, left column, noting in particular the mention of release of water molecules from the cyclodextrin cavity as a driving force for drug-cyclodextrin complex formation).

(c) The complexes have different properties from mere physical mixtures of drugs and cyclodextrins, for example in terms of drug solubilization and drug stabilization (pages 1020-1024), a fact shown for HP β CD and cladribine in the Van Axel Castelli et al. article discussed below.

(d) The amorphous cyclodextrins such as HP β CD have almost countless isomeric and variably substituted forms and upon complexation result in amorphous products which are mixtures of countless complexes (page 1018, left column, line 12 from the bottom, to page 1018, right column line 2).

To address applicants' position that use of cladribine in Baert et al.'s melt extrusion product is inappropriate because of the fact that the decomposition temperature of cladribine is lower than the Baert et al. process's temperature, the Examiner has cited several additional documents (the Britannica Online excerpt and

the two Suzuki et al. articles). Applicants believe that these documents are irrelevant for at least the following reasons:

(a) These references relate to freezing point depression and teach nothing about decomposition of cladribine at the high temperatures used in the Baert et al. process.

(b) These references relate only to crystalline cyclodextrins (α - and β -cyclodextrin), which give crystalline complexes from water and not to amorphous cyclodextrins such as HP β CD, which give amorphous complexes from water, these different kinds of complexes exhibiting different properties; moreover, neither Schultz et al. nor Baert et al. even remotely suggest that their solid oral dosage forms contain cyclodextrin/drug complexes, both characterizing their solid products as mixtures.

(c) The experimental data provided in the Van Axel Castelli et al. article and discussed below prove that cladribine and an amorphous cyclodextrin such as HP β CD do not form an eutectic mixture; rather, Van Axel Castelli et al. as discussed below, shows that cladribine, whether in a complex or in a mixture with HP β CD, decomposes at temperatures far below those used for this cyclodextrin in the Baert et al. process.

Turning to the Van Axel Castelli et al. article, which was discussed in detail by Dr. Bodor at the interview, a further copy of which is provided herewith and which is listed on the accompanying form PTO-1449, the following remarks are offered:

The Van Axel Castelli et al. article shows that an inclusion complex of cladribine and 2-hydroxypropyl- β -cyclodextrin has properties which are different from those of the cyclodextrin, those of cladribine and those of physical mixtures of the cyclodextrin with cladribine. These differences were discussed at length by Dr. Bodor at the interview with respect to various analyses conducted by Van Axel Castelli et al. and can be summarized as follows:

(a) Thermo gravimetric analysis (TGA) was conducted over the temperature range from 25°C to 360°C for (a) cladribine, (b) HP β CD, (c) their inclusion complex and (d) their physical mixture and the results are shown in Fig. 2. Fig. 2a, the TGA curve for cladribine itself, shows decomposition of cladribine starting at about 200°C. Fig. 2b, the TGA curve for HP β CD, shows a mass loss of

6% at 30°C to about 140°C, due to dehydration, and decomposition at about 300°C. Fig. 2c, the TGA curve for the cladribine/HP β CD complex, shows water loss between 20°C and 100°C and a decomposition process starting at about 250°C. Fig. 2d, the TGA curve for the cladribine plus HP β CD physical mixture, shows a multi-stage decomposition pathway; the first decomposition stage between room temperature and 100°C is due to loss of water from the cyclodextrin, whereas the second decomposition stage, observed at temperatures above 200°C, is due to the decomposition of cladribine. Fig. 2d also shows that heating the mixture to high temperatures does not lead to complexation but rather to decomposition of cladribine. Comparing the TGA for the complex with that of the physical mixture shows a slower degradation for the complex than for the mixture. Nevertheless, cladribine, whether in a complex or in a mixture with HP β CD, decomposes at temperatures far below those used for HP β CD-containing products in the Baert et al. process.

(b) Differential scanning calorimetry (DSC) analysis was conducted and the results shown in Fig. 3 for (a) cladribine, (b) HP β CD, (c) cladribine/HP β CD complex, (d) cladribine plus HP β CD physical mixtures, and (e) cladribine plus HP β CD kneading product. The authors note that the DSC trace of cladribine shows two endothermic events (Fig. 3a), the first at 206.3°C being close to the cladribine decomposition onset temperature and corresponding to the melting transition, and the second at 211.9°C, which is during the decomposition process, and probably is due to a decomposition product of cladribine. The DSC profile for the cyclodextrin (Fig. 3b) confirms an endothermic event corresponding to water loss from about 40°C to about 100°C. The authors further note that the DSC curves of the inclusion complex (Fig. 3c), physical mixture (Fig. 3d) and kneading product (Fig. 3e) all show a broad thermal event from about 40 to 140°C, due to water loss in the cyclodextrin. In addition, the physical mixture and the kneading product are observed to feature two endothermic events around 200°C; these can be attributed to free cladribine in the mixture and kneading product. In contrast, Fig. 3c, the DSC trace for the complex, shows only one endothermic event, which occurs in the high temperature region, at 234.5°C; this is considerably higher than the degradation onset of pure cladribine around 200°C (Fig. 2a), while the latter also characterizes the mixtures. As

noted by the authors, the absence of thermal events typical of pure cladribine shows a loss of cladribine crystalline character for the complex. This also confirms DSC data for the products of instant Examples 1 and 2 reported on page 31 of the instant specification and correlates well with applicants' x-ray diffraction traces for the products of Examples 1 and 2 reported on page 31 of the specification, where no peaks for crystalline cladribine were found in the complexes;

(c) FT-IR and FT-Raman spectroscopy were also recorded by Van Axel Castelli et al. In Figures 5 and 6, the FT-IR and FT-Raman spectra of cladribine alone (a), cladribine/cyclodextrin physical mixture (b), cladribine/cyclodextrin complex (c) and cyclodextrin alone (d) were compared. The authors indicate that the IR spectrum of the physical mixture (Fig. 5b) can be interpreted as the sum of the spectra for pure crystalline cladribine (Fig. 5a) and pure HP β CD (Fig. 5d), also supported by Fig. 6. The authors continue:

In contrast, both IR and Raman spectra of the inclusion complex show clear differences with respect to those of the physical mixture. In particular, markers of the crystalline phase of cladribine (arrows on Figs. 4 and 5) cannot be found in the spectra of the inclusion complex.

The authors further find that their data suggest that, when part of an inclusion complex, cladribine is present in a different (non-crystalline) phase relative to that of pure crystalline cladribine and that direct interaction between cladribine molecules is prevented. Further, they note that the amorphous phase has to be attributed to the formation of molecular complexes where the interaction between cladribine and HP β CD shields cladribine molecules, thus preventing crystallization.

(d) Van Axel Castelli et al. also used nuclear magnetic resonance spectroscopy to better understand the molecular interactions in the cladribine/cyclodextrin complex. To obtain direct proof of complex formation, the authors conducted a 2D ROESY experiment, the results of which showed a typical inner portion of HP β CD, confirming that a host-guest inclusion complex had formed between cladribine and HP β CD. Further, the authors conducted ^{13}C CP-MAS NMR experiments and reported the spectra in Fig. 10 for cladribine (a), cladribine +

HP β CD physical mixture (b) and cladribine/ HP β CD complex (c). In the cladribine spectrum (Fig. 10a), the authors observed sharp peaks due to cladribine's high degree of crystallinity. The spectrum for the physical mixture (Fig. 10b) corresponds to the sum of the spectra of the two components, with no resonance peaks or line broadening, showing no intermolecular interaction in the mixture, the solid being composed of distinct ordered domains of each component. In the spectrum for the complex, no shift in the HP β CD signals are detected, whereas the cladribine resonances are broadened and only slightly detectable. The authors note that this indicates that no crystalline domains of cladribine are present.

(e) Van Axel Castelli et al. also conducted DSC and TGA thermal profiles for tablets of the cladribine/ HP β CD complex and found them comparable to those for the cladribine/ HP β CD complex itself. Moreover, even stressed tablets showed no notable differences in the DSC thermal profile, which demonstrated that they were storage stable even under less than ideal conditions.

(f) Van Axel Castelli et al. conclude that thermal analyses, vibrational analyses, and solid-state NMR all indicate that cladribine behaves differently when in the complex compared with the physical mixture or kneading product, while ROESY provides evidence for the existence of an internal complex between cladribine and HP β CD. They further conclude that tablets of the complex are not affected by their manufacturing from the complex itself and are storage stable. These tablets have been used in a successful clinical trial for oral treatment of patients with MS (CLARITY trial).

Information about the clinical trials of this product was presented at the interview and copies of several articles appearing on the internet are appended and listed on the accompanying Form PTO-1449. The product is expected to be the first marketed oral product for the treatment of multiple sclerosis.

In summary, applicants submit that the obviousness rejection based on Schultz et al. in view of Baert et al. is untenable and should be withdrawn. The data provided by Van Axel Castelli et al. conclusively show that cladribine, whether alone, in a physical mixture with HP β CD, or even in a cladribine/HP β CD complex, decomposes at temperatures far lower than those used by Baert et al. for melt extruding drugs with the same cyclodextrin. The data further show that heating a

physical mixture of cladribine with HP β CD to high temperatures does not result in a complex of cladribine and in fact the cladribine in the mixture decomposes long before the melting point for HP β CD is reached. Thus, the Baert et al. process is not suitable for making a melt extrudate of cladribine with hydroxypropyl- β -cyclodextrin and moreover such a product prepared according to Baert et al. would not contain a complex of cladribine with the cyclodextrin as claimed in this application. The Schultz et al. oral dosage form prepared by the Baert et al. process simply cannot contain a cladribine/cyclodextrin complex.

Claims 82-98 are drawn to a product-by-process. These claims have been amended above and now depend directly or indirectly from Claim 1 and thus contain all of the Claim 1 limitations. Applicants have shown that the Claim 1 composition is free of the art, therefore, the product-by-process claims are also patentable over the art.

CONCLUSION

In view of the foregoing, it is believed that all record rejections have been overcome. Further, favorable action in the form of a Notice of Allowance is believed to be in order and is earnestly solicited.

In the event that there are any remaining issues which could be resolved in a telephone discussion, the Examiner is urged to telephone the undersigned at the number given below so that such issues can be promptly resolved.

Respectfully submitted,

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